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The role of Chlamydia in coronary heart disease—fact or fiction?

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Introduction

Atherosclerosis is an inflammatory disease. A number of traditional and non-traditional risk factors related to atherogenesis have been identified. Much of the attributable risk remains unexplained, however, the complex aetiology of atherosclerosis has not yet been entirely dissected. Pathologically, atherosclerosis involves injury, inflammation, infiltration, degeneration, and thrombosis [1]. In patients at risk a role for the local inflammatory response in plaques as well as systemic inflammation has been recognized and documented [2]. Several authors raised the possibility that infectious agents directly or indirectly trigger the cascade of biological and biochemical reactions leading to inflammation, atherosclerosis, and vascular thrombotic events [3].

A group of infective agents called Chlamydia has given pathologists a series of surprises. Once known mainly for causing illness in parrots, they turned out to be responsible for several sexually transmitted diseases. Distinct from most chlamydial species, *C. pneumoniae* is a human pathogen [4]. Epidemiological studies have identified *C. pneumoniae* as the third most common aetiologic agent of bronchitis and pneumonia and antibody prevalence studies suggest that more than 50% of adults have been exposed to it. Research in this field has received a shot in the arm by the unanticipated discovery of *Helicobacter pylori* as the infectious aetiologic agent of another chronic inflammatory illness, i.e. peptic ulcer disease. Whether *C. pneumoniae* or other infectious agents are a cause, a cofactor, or an innocent commensal in the genesis of atherosclerotic plaques is therefore a matter of intensive research and debate.

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Where is the link between atherosclerosis and *C. pneumoniae*?

A hint for a link between *C. pneumoniae* and atherosclerosis first came from seroepidemiological studies from Finland [5]. Meanwhile a number of studies have shown associations between *C. pneumoniae* seropositivity and atherosclerosis either of the carotid arteries or of the coronary circulation [6,7]. These studies were retrospective and cross-sectional, however, and thus fail to provide definite proof. Although a high prevalence of anti-chlamydial antibodies has consistently been found in patients with ischaemic heart disease, the predictive value is limited given the high level of exposure in the general adult population [8]. For the same reason the issue of causality remains unresolved, since anti-chlamydial antibodies are found in 50% of the middle aged population. Furthermore, two recent studies revealed conflicting results: while an association of seropositivity for *C. pneumoniae* with an increased risk of future cardiovascular disease could be demonstrated in hypertensive patients [9], a large-scale prospective study controlled for cardiovascular risk factors failed to provide evidence for an association between *C. pneumoniae* IgG seropositivity and the risk of future myocardial infarction [10].

Does histopathology support serology?

More compelling than seroepidemiologic association has been the finding of bacterial antigen, and less commonly other biological evidence for *C. pneumoniae*, within atherosclerotic tissues of carotid [11,12] or coronary plaques [13,14]. Evidence for the existence of the organisms in atherosclerotic tissue has been presented by means of various techniques (PCR, immunohistology, microimmunofluorescence, electron microscopy, culture). Locally demonstratable Chlamydiae are not consistently accompanied by positive serology, however. Meanwhile, the presence of Chlamydiae within atherosclerotic lesions is beyond any doubt, but whether *C. pneumoniae* is an 'innocent bystander' or has a direct causative role in the development of coronary artery disease remains to be determined.

Which mechanisms could be pathophysiologically relevant?

A number of *in vivo* and *in vitro* studies have been performed to elucidate potential pathomechanisms how colonization of the arterial wall with *C. pneumoniae* might contribute to the development of atherosclerosis. Data revealed that *C. pneumoniae* can infect mononuclear phagocytes [3] and vascular endothelial cells. This causes foam-cell formation and expression of procoagulant activity respectively. *C. pneumoniae* is capable to survive and multiply within cells of the human vascular wall. It can provoke cytokine production and this in turn may lead to instability of the atherosclerotic plaque [15]. Recent data identified antigenic mimicry [16] and antibodies against chlamydial heat shock protein [17] as possible mediators of Chlamydia-induced damage. Despite such recent progress there is still no definite proof that these potential pathogenetic mechanisms really contribute to the initiation or progression of atherosclerotic plaques.

What can we learn from therapeutic studies?

Chronic inflammatory/degenerative diseases that were previously thought to be non-infectious may indeed be infectious and treatable with antibiotics. The best example is the response of peptic ulcer disease to antibiotic therapy directed at *H. pylori* [18].

Chlamydiae, including *C. pneumoniae*, are generally sensitive to antibiotic therapy with macrolides and tetracyclines. Azithromycin, a new macrolide antibiotic, is rapidly absorbed and widely distributed into tissues, where it achieves persistently high concentrations. Administered to cholesterol fed rabbits, azithromycin prevented the acceleration of atherosclerosis induced by *C. pneumoniae* [19]. In a pilot clinical study, Gupta *et al.* [20] treated 60 survivors of myocardial infarction with brief courses of azithromycin and achieved a decrease in selected markers of inflammation (CRP, IL-6) and, in parallel, of anti-chlamydial antibody titres and clinical events. In line with these findings, the ROXIS study also showed a lower incidence of acute ischaemic events in 102 patients with unstable angina treated with roxithromycin [21]. Recently clarithromycin was shown to decrease fibrinogen levels in patients with ischaemic heart disease [22]. In addition, another prospective, randomized, secondary prevention study, named ACADEMIC trial, documented improvement in four markers of inflammation (CRP, IL-1, IL-6, TNF) in 150 patients on azithromycin therapy. Disappointingly, however, no di erences in antibody titres and clinical events were observed [23]. Unfortunately, the above studies do not resolve the issue whether the beneficial e ect of macrolides was caused by eradication of *C. pneumoniae*, or as a result of their non-specific anti-inflammatory e ects.

How can causality be proved?

In order to establish a direct etiologic link between disease and infecting agent, a number of criteria must be met which are known as 'Koch's postulates': (i) the microorganism must be present in all or nearly all cases of the disease, (ii) inoculation of pure cultures must reproduce the disease (for example, when injected into susceptible animals), and (iii) it must again be possible to obtain and propagate pure cultures of the agent from the diseased organism.

Of these, the first postulate appears to be fulfilled by Chlamydia species in atherosclerotic coronary heart disease. But it is di cult to cause atherosclerosis by

infection with *C. pneumoniae*. Nevertheless, in two animal studies intranasal infection of rabbits with *C. pneumoniae* was shown to induce or accelerate atherosclerosis [19]. However, these findings are limited by a recent study in LDL-receptor gene deficient mice, in which hypercholesterolemic conditions were required for *C. pneumoniae* to aggravate the development of atherosclerosis [24]. Ultimately, large controlled and prospective clinical trials will be required to prove or disprove a causal relation between prior infection with *C. pneumoniae* and atherosclerosis [25].

Is there a link in the renal patient?

Cardiovascular disease is the most prominent cause of morbidity and mortality in patients with chronic renal disease and patients on renal replacement therapy. A number of traditional and non-traditional, i.e. uraemia related cardiovascular risk factors have been identified. Interestingly, markers of microinflammation or infection, such as serum concentrates of C-reactive protein or serum amyloid A identify haemodialysis patients at risk of cardiovascular complications and death. Serum levels of these markers are ten-fold higher in predialysis or haemodialysis patients than in healthy controls [26,27]. The cause(s) of the high levels of acute phase reactants in blood are unknown, but it is tempting to speculate that the acute phase response reflects *C. pneumoniae* infection. It is generally intellectually attractive to reduce the complexity of observations by defining relatively simple pathogenetic relationships. It is therefore attractive to explain the frequency of cardiovascular damage in immunoincompetent (uraemic) patients by *C. pneumoniae* infection. Indeed, a recent cross-sectional study showed that high anti-chlamydial IgG titres are associated with elevated CRP levels in predialysis patients [28].

Conclusions

At the present state of knowledge only few firm statements on the relation between atherosclerosis and Chlamydia can be made.

- Coronary heart disease is associated with antibodies against *C. pneumoniae*.
- *C. pneumoniae* can be detected in a high proportion of atherosclerotic plaques.
- Treatment with macrolides improves markers of inflammation in coronary heart disease.
- Target cells of atherosclerosis can be infected by *C. pneumoniae in vitro*.

Taken together, the available data suggest some kind of relationship between *C. pneumoniae* and atherosclerosis. It remains unclear, however, whether Chlamydia initiates atherosclerotic injury, facilitates its progression, or merely colonizes pre-existing atherosclerotic plaques. Much more carefully conducted studies are necessary to definitely answer these questions in the future.

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